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Concise report

# Different disease subtypes with distinct clinical expression in familial Mediterranean fever: results of a cluster analysis

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## Abstract

**Objective.** The aim of this study was to evaluate whether there are clinical subgroups that may have different prognoses among FMF patients.

**Methods.** The cumulative clinical features of a large group of FMF patients [1168 patients, 593 (50.8%) male, mean age 35.3 years (S.D. 12.4)] were studied. To analyse our data and identify groups of FMF patients with similar clinical characteristics, a two-step cluster analysis using log-likelihood distance measures was performed. For clustering the FMF patients, we evaluated the following variables: gender, current age, age at symptom onset, age at diagnosis, presence of major clinical features, variables related with therapy and family history for FMF, renal failure and carriage of M694V.

**Results.** Three distinct groups of FMF patients were identified. Cluster 1 was characterized by a high prevalence of arthritis, pleuritis, erysipelas-like erythema (ELE) and febrile myalgia. The dosage of colchicine and the frequency of amyloidosis were lower in cluster 1. Patients in cluster 2 had an earlier age of disease onset and diagnosis. M694V carriage and amyloidosis prevalence were the highest in cluster 2. This group of patients was using the highest dose of colchicine. Patients in cluster 3 had the lowest prevalence of arthritis, ELE and febrile myalgia. The frequencies of M694V carriage and amyloidosis were lower in cluster 3 than the overall FMF patients. Non-response to colchicine was also slightly lower in cluster 3.

**Conclusion.** Patients with FMF can be clustered into distinct patterns of clinical and genetic manifestations and these patterns may have different prognostic significance.

**Key words:** familial Mediterranean fever, cluster analysis, marenostrin, phenotype.

**Rheumatology key message**

- There may be clusters of patients in FMF with different characteristics and different prognoses.
- Disease clusters in FMF may help ufnote_rules better understand disease pathogenesis and therapy.

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## Introduction

FMF is an auto-inflammatory disease characterized by self-limited attacks of fever and serositis [1]. In different ethnic groups and individuals its manifestations vary substantially, and the disease may change its course over time. Moreover, disease expression may be different in different ethnic groups. In Armenian and Japanese patients, the second most common manifestation was reported as pleuritis [2, 3]. Joint involvement was found to be more common among non-Ashkenazi Jews than in Turks, Arabs and Armenians [3–6].

Following the discovery of the causative gene called *MEFV*, numerous studies have evaluated the genotype/phenotype correlations in different populations. Patients with certain *MEFV* mutations may have more severe disease and a greater chance of developing amyloidosis [7]. Homozygosity for M694V was reported to be associated with earlier age of disease onset, higher frequency of arthritis, higher dose of colchicine needed for controlling attacks and higher rate of amyloidosis in most of the populations [7–9]. However, genotype/phenotype studies could not entirely explain the different clinical presentations between different ethnic groups.

Cluster analysis is a statistical procedure that allows the researcher to identify groups of individuals due to their differences. Clustering and generating an algorithm not only constitute genotype/phenotype correlations, but also provide an opportunity to incorporate genotype data beside phenotype data. Awareness of these clusters may provide us a better understanding of the disease behaviour. The demonstration of the subgroups characterized by a similar treatment response pattern or similar prognosis may also allow the design of appropriate studies to reveal genetic or environmental modifiers. Therefore the aim of this study was to evaluate whether there are clinical subgroups, which may have different prognoses, among Turkish FMF patients.

## Materials and methods

### Design and patients

With the permission of the local ethics committee, we evaluated all adult FMF patients according to the diagnostic criteria suggested by Livneh *et al*. [10] followed up in two tertiary teaching hospitals. A total of 1168 FMF patients [593 (50.8%) male with a mean age of 35.3 years (S.D. 12.4)] were identified. The following data were collected from medical records by using a structured form: demographic characteristics (age, sex, parental consanguinity, work status), age at the onset of attacks, age at diagnosis, cumulative clinical features of FMF, presence of amyloidosis, colchicine use, colchicine dosage, compliance with treatment, response to colchicine and family history. Patients' *MEFV* gene status was also recorded. This work was approved by the ethics committee of Izmir Kâtip Çelebi University.

### Statistical analysis

Unless otherwise stated, values are presented as the mean (S.D.) or the percentage as appropriate. To analyse our data and identify groups of FMF patients with similar clinical characteristics, a two-step cluster analysis using log-likelihood distance measures was performed. For clustering the FMF patients, we evaluated the following variables: gender, current age, age at symptom onset, age at diagnosis, the presence of major clinical features [fever, peritonitis, pleuritis, arthritis, erysipelas-like erythema (ELE), febrile myalgia, amyloidosis], variables related with therapy (dosage of colchicine, compliance with therapy and the presence of attacks despite colchicine usage), family history for FMF and renal failure and the presence of the M694V allele. For all measurements, a $P$-value $< 0.05$ was considered statistically significant. All statistical analyses were performed by using Statistical Package of Social Science (SPSS), version 13.0 (Chicago, IL, USA).

**Table 1** The demographic and disease-related characteristics of FMF patients ($n = 1168$)

| Characteristic | Value |
|---|---|
| Female, % | 49.2 |
| Current age, mean (S.D.), years | 35.3 (12.4) |
| Age at symptom onset, mean (S.D.), years | 14.9 (9.3) |
| Age at diagnosis, mean (S.D.), years | 25.9 (11.7) |
| Compliance to colchicine treatment, % | 90 |
| Colchicine dosage, mean (S.D.), mg | 1.4 (0.4) |
| Fever, % | 97 |
| Peritonitis, % | 96 |
| Pleuritis, % | 64 |
| Arthritis, % | 52 |
| Erysipelas-like erythema, % | 30 |
| Protracted febrile myalgia, % | 16 |
| Amyloidosis, % | 9 |
| Attacks despite colchicine use, % | 46 |
| Family history of FMF, % | 55 |
| Family history for renal failure, % | 15 |
| Presence of the M694V allele, % | 69 |

## Results

Demographic and some of the clinical characteristics of the patients are summarized in the Table 1. A two-step cluster algorithm selected three clusters in this analysis and 679 patients (58%) with valid information for all variables were included in the cluster formation. The size of each cluster and statistically significant individual predictors sorted by overall importance for the cluster formation are shown in Table 2. As is demonstrated in Table 2, 10 of the 17 variables included in the algorithm were predicted by the clusters.

### Cluster features

Patients in cluster 1 were characterized by a high prevalence of febrile myalgia, ELE and pleurisy. The family history of FMF was slightly lower in this group. Although the dosage of colchicine was lower and colchicine resistance was more frequent, the frequency of amyloidosis was not high among these patients. Patients in cluster 2 had an earlier age of disease onset and a higher frequency of family history for FMF. The M694V carriage and amyloidosis prevalences were highest in cluster 2. The mean colchicine dosage was also higher in these patients.

Cluster 3 was characterized by the lowest prevalence of arthritis, febrile myalgia and ELE. We also found that the frequencies of M694V carriage and amyloidosis were lower in cluster 3 than the overall cohort. Colchicine resistance was also slightly lower in this cluster.

**Table 2** Cumulative disease features of three clusters of FMF patients

| Feature | Cluster 1 | Cluster 2 | Cluster 3 |
|---|---|---|---|
| Cluster size, *n* (%) | 108 (15.9) | 302 (44.5) | 269 (39.6) |
| Arthritis, % | 100 | 91 | 9 |
| Protracted febrile myalgia, % | 100 | 14 | 2 |
| Erysipelas-like erythema, % | 96 | 41 | 2 |
| Presence of the M694V allele, % | 74 | 86 | 48 |
| Mean age at symptom onset, years | 17.5 | 11.3 | 17.9 |
| Mean colchicine dosage, mg | 1.1 | 1.5 | 1.4 |
| Attacks despite colchicine use, % | 81 | 52 | 38 |
| Pleuritis, % | 95 | 58 | 59 |
| Amyloidosis, % | 2 | 17 | 4 |
| Family history of FMF, % | 38 | 62 | 46 |

## Discussion

The cluster analysis algorithm may be an appropriate procedure for examining clinical and genetic subgroups in heterogeneous disorders like FMF. To our knowledge there has been no previous work using cluster analysis to evaluate disease subgroups in FMF. The present study revealed that there may be distinct clusters of FMF patients with distinct patterns of clinical expression and prognosis.

In a previous study we observed that amyloidosis was associated with male sex, arthritis, a family history of amyloidosis and an M694V homozygous genotype in a large group of FMF patients [9]. The present work also confirmed that FMF patients in cluster 2 who have a high frequency of amyloidosis were characterized by a higher ratio of M694V carriage. These patients also have high frequency of arthritis. To support these findings our cluster algorithm revealed that the group of patients (cluster 3) with a very low frequency of arthritis, ELE, protracted febrile myalgia and low prevalence of M694V carriage have a low risk of developing amyloidosis. Despite the fact that we could not find any significant contribution of age at diagnosis in the clustering algorithm, it can be hypothesized that diagnostic delay may contribute to the higher amyloidosis frequency in cluster 2, since age at symptom onset is lowest in this group. Thus taking precautions regarding diagnostic delay may improve the amyloidosis risk.

However, rather surprisingly, we also showed that there may be a small group of FMF patients with arthritis carrying the M694V allele, but with a lower probability of developing amyloidosis (cluster 1). Moreover, the findings that the use of lower doses of colchicine and the relatively more frequent colchicine resistance among the members of cluster 1 suggested that the final phenotype is not determined by *MEFV* alone, but may be a function of other genetic or environmental modifying factors [11]. Previously it was shown that the alpha allele of the *SAA* gene [12] affects the disease course by predisposing individuals to the development of amyloidosis. Other genes that can affect disease severity include the *MICA* and *NOD2/CARD15* genes [11, 13, 14].

The main limitation of our study is the retrospective nature of the analysis. Because of missing data for clinical and laboratory variables, we were able to include only ~60% of the cases that were followed up. On the other hand, certain features having prognostic significance, like age at disease onset, the frequency of amyloidosis and M694V carriage, were similar between patients included and excluded from the analysis. We did not include information about other modalities of treatment that may influence the disease course, such anti-IL-1 drugs [15], because of their rarity at the time of data collection. The sample size of the present study did not allow us to test the importance of other *MEFV* mutations. It would be interesting to extend our findings using a cluster analysis in a larger, prospective and multi-ethnic cohort with complete clinical, genetic and therapeutic data. And the inclusion of survival and possible genetic and environmental modifiers may provide a more robust opportunity to cluster patients with such a heterogeneous disorder.

In conclusion, the results of this study suggest that there may be subgroups of FMF patients with different clinical and genetic characteristics and different prognoses. This clustering may help physicians detect modifying factors other than *MEFV* and treat patients more appropriately.

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